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Boehringer Ingelheim
Pharmaceuticals Inc.

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1601
Rockville, MD 20857

April 16,1999

[Docket No. 99D-0121] Draft Guidance for Industry on Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Containing Certain Active Moieties/Active Ingredients Based on a Biopharmaceutics Classification System

Patricia Watson
Telephone 203-791-6233
Telefax 203-791-6262
E-Mail pwatson@bi-pharm.com

900 Ridgebury Rd/P.O. Box 368
Ridgefield, CT 06877-0368
Telephone (203) 798-9988

Dear Sir or Madam:

Boehringer Ingelheim appreciates the opportunity to give comments on the subject draft guidance. Our comments are set out below the referenced page and section number of the draft guidance.

Pages 2 – 3
Section III. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The Biopharmaceutics Classification System (BCS) suggests for high solubility, high permeability drugs (Case 1), that 85% dissolution in 0.1 N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution. In such cases, gastric emptying (around 15 – 20 minutes in the fasted state) becomes the rate limiting step to drug absorption.

The subject draft guidance suggests that a *rapidly dissolving* IR dosage form containing a Case 1 drug, is one where 85% of the label claim of the drug substance dissolves within 30 minutes in three recommended dissolution media. It is not clear why dissolution profile in three different pH media are considered necessary, since the solubility of the drug substance over the pH range 1 – 8 will have been established. If the drug is *highly soluble* over the pH 1 – 8 range, then the disintegration of the dosage form, rather than the dissolution rate of the drug substance, becomes the important factor to drug absorption.

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Pages 6 – 7
SECTION V. REQUESTING A WAIVER OF IN VIVO BA/BE STUDIES

We suggest that an additional condition for a biowaiver be that the drug should not be characterized by a pronounced pre-systemic elimination / first pass metabolism and /or non-linear pharmacokinetics within the therapeutic range.

Sincerely,

Patricia Watson

Patricia Watson
DRA Technical Director
Drug Regulatory Affairs

Boehringer Ingelheim

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